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Diagnosis and Management of Cardioembolic Stroke

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ABSTRACT

OBJECTIVE: **Cardioembolic stroke accounts for nearly 30% of ischemic strokes. Prompt diagnosis of the underlying mechanism may improve secondary prevention strategies. This article reviews recent randomized trials, observational studies, case reports, and guidelines on the diagnosis and treatment of cardioembolic stroke.**

LATEST DEVELOPMENTS: **Several pathologies can lead to cardioembolic stroke, including atrial fibrillation, aortic arch atheroma, patent foramen ovale, left ventricular dysfunction, and many others. Secondary stroke prevention strategies differ across these heterogeneous mechanisms. In addition to medical treatment advances such as the use of direct oral anticoagulants in patients with atrial fibrillation, surgical treatments such as closure of patent foramen ovale have been shown to reduce the risk of recurrent stroke in select patients. Furthermore, left atrial appendage occlusion is a promising strategy for patients with atrial fibrillation who are candidates for short-term oral anticoagulation therapy but not long-term oral anticoagulation therapy.**

ESSENTIAL POINTS: **A thorough diagnostic evaluation is essential to determine cardioembolic causes of stroke. In addition to risk factor management and lifestyle modifications, identification and targeting of the underlying cardioembolic stroke mechanisms will lead to improved stroke prevention strategies in patients with cardioembolic stroke.**

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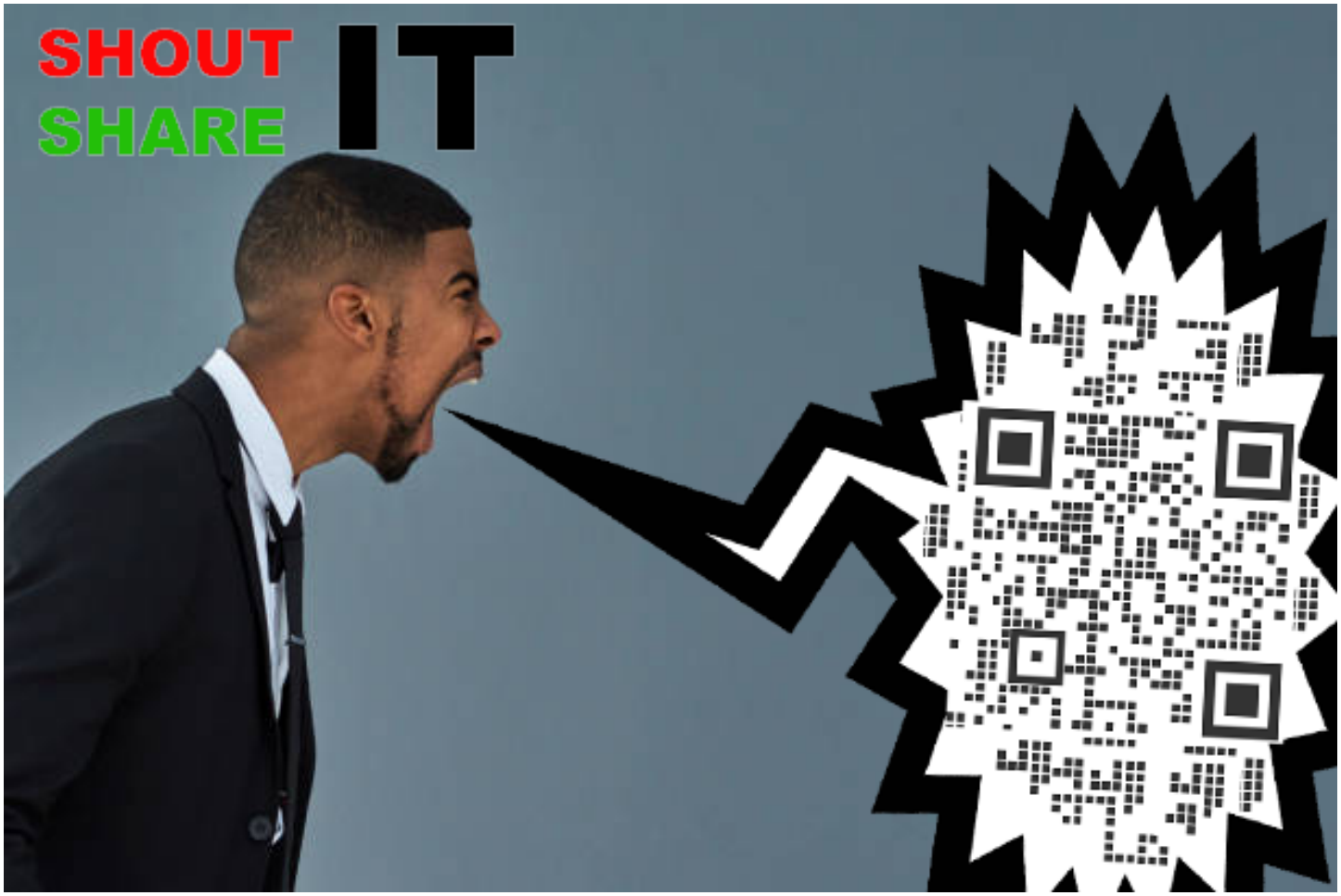
INTRODUCTION

Cardioembolic stroke accounts for nearly 30% of ischemic strokes and is associated with increased morbidity and mortality.[1,2] Several cardiac pathologies can lead to ischemic stroke, and these include high-risk cardiac sources such as atrial fibrillation, endocarditis, and left ventricular thrombus, as well as lower-risk cardiac sources such as patent foramen ovale.[1,2] While secondary prevention strategies in cardioembolic stroke have improved over the past decades, gaps in knowledge remain. In addition to risk factor control, which is the basis of secondary stroke prevention, identifying and targeting the stroke mechanism is a key element of secondary prevention. This is particularly important in patients with acute cardioembolic stroke given the wide range of potential mechanisms. This article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provides an overview of specific cardioembolic sources and discusses secondary prevention strategies in these patients.

KEY POINT

● Direct oral anticoagulants are at least as effective as warfarin in stroke prevention in atrial fibrillation and have lower risk of intracranial hemorrhage.

EVALUATION OF PATIENTS WITH SUSPECTED CARDIOEMBOLIC STROKE

In patients with suspected cardioembolic stroke (ie, embolic-appearing infarct on imaging but no cardiac source identified on initial diagnostic evaluation), a transesophageal echocardiogram and prolonged outpatient cardiac rhythm monitoring may be considered to identify cardiac sources, which may lead to a change in clinical management. For instance, identifying paroxysmal occult atrial fibrillation on outpatient cardiac monitoring leads to anticoagulation therapy, and identification of a patent foramen ovale may lead to consideration of closure. A transesophageal echocardiogram can also identify less common cardioembolic sources such as cardiac myxoma or fibroelastoma that may require surgery. This topic is discussed in more detail in the article "Diagnostic Evaluation of Stroke Etiology," by James F. Meschia, MD, FAAN, in this issue of *Continuum*.[3]

ATRIAL FIBRILLATION

Atrial fibrillation is the most common heart arrhythmia, affecting nearly 2% of the general population in a European study, with increased incidence in older adults.[4] Atrial fibrillation is divided into two categories: valvular atrial fibrillation (defined as atrial fibrillation in the setting of moderate to severe mitral valve stenosis or mechanical valve replacement) and nonvalvular atrial fibrillation.[5] The incidence of atrial fibrillation is increasing with the aging population and improved detection tools. In one study incidence rates by year increased from a minimum of 4.74 per 1000 person-years in 2008 to 6.82 per 1000 person-years in 2018.[5] Studies have shown an association between atrial fibrillation and ischemic stroke and cardiovascular death.[6] In patients with atrial fibrillation, clinical variables associated with increased stroke risk include age, female sex, hypertension, diabetes, congestive heart failure, history of stroke or transient ischemic attack (TIA), and evidence of atherosclerotic disease.[6] Furthermore, using these clinical variables, the $CHADS_2$ score (**c**ongestive heart failure, **h**ypertension, **a**ge 75 years or older, **d**iabetes mellitus, and previous **s**troke or TIA) and CHA_2DS_2VASc score ($CHADS_2$ plus **v**ascular disease, **a**ge 65 to 74 years, and **s**ex **c**ategory [female]) can aid in risk-stratifying patients and selecting those who may benefit from anticoagulation therapy. In addition to clinical variables, laboratory variables (eg, N-terminal pro b-type natriuretic peptide or high-sensitivity cardiac troponin) and cardiac biomarkers (eg, atrial fibrillation burden, fibrosis, atrial enlargement, or left atrial appendage morphology) have been identified as predictors of stroke risk in atrial fibrillation but are not currently widely utilized to risk-stratify patients.[6]

Secondary stroke prevention in patients with atrial fibrillation encompasses medical and surgical treatment options and is somewhat different from other subtypes. While risk factor management and lifestyle changes are of importance, studies have shown the superiority of warfarin over aspirin therapy for primary and secondary stroke prevention in patients with atrial fibrillation.[7,8] Over the past decade, randomized trials showed that direct oral anticoagulants are at least as effective as warfarin in stroke prevention in atrial fibrillation and have lower risk of intracranial hemorrhage (TABLE 4-1[9]).[10-12] Furthermore, the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment)

trial[13] compared apixaban to aspirin in patients deemed unsuitable for warfarin and was stopped early due to a significant reduction in stroke risk with apixaban without increased risk of intracranial hemorrhage (TABLE 4-1).

On the other hand, in patients with valvular atrial fibrillation, warfarin is the preferred treatment since the above-mentioned trials were limited to nonvalvular atrial fibrillation and the RE-ALIGN (Dabigatran Etexilate in Patients With Mechanical Heart Valves) randomized trial[14] comparing dabigatran to warfarin in

TABLE 4-1 **Major Recent Stroke Prevention Trials in Atrial Fibrillation[a]**

Study	Patient population	Comparator groups	Stroke or systemic embolism	Major hemorrhage
RE-LY (open label)	Mean age: 71 years Mean $CHADS_2$ score: 2.1 Mean TTR: 64% History of stroke or TIA: 20%	Dabigatran 150 mg Dabigatran 110 mg Warfarin	Dabigatran 150 mg versus warfarin: risk ratio 0.66; 95% confidence interval, 0.53 to 0.82 Dabigatran 110 mg versus warfarin: risk ratio 0.91; 95% confidence interval, 0.74 to 1.11	Dabigatran 150 mg versus warfarin: risk ratio 0.93; 95% confidence interval, 0.81 to 1.07 Dabigatran 110 mg versus warfarin: risk ratio 0.80; 95% confidence interval, 0.69 to 0.93
ROCKET-AF (randomized controlled)	Mean age: 73 years Mean $CHADS_2$ score: 3.5 Mean TTR: 55% History of stroke, systemic embolism, or TIA: 55%	Rivaroxaban 20 mg Warfarin	Rivaroxaban versus warfarin: hazard ratio 0.88; 95% confidence interval, 0.75 to 1.03	Rivaroxaban versus warfarin: hazard ratio 0.69; 95% confidence interval, 0.90 to 1.20
ARISTOTLE (randomized controlled)	Mean age: 70 years Mean $CHADS_2$ score: 2.1 Mean TTR: 62% History of stroke, systematic embolism, or TIA 19.4%	Apixaban 5 mg Warfarin	Apixaban versus warfarin: hazard ratio 0.79; 95% confidence interval, 0.66 to 0.95	Apixaban versus warfarin: hazard ratio 0.69; 95% confidence interval, 0.60 to 0.80
ENGAGE (randomized controlled)	Median age: 72 years Mean $CHADS_2$ score: 2.8 Median TTR: 68% History of stroke or TIA: 28%	Edoxaban 60 mg Edoxaban 30 mg Warfarin	Edoxaban 60 mg versus warfarin: hazard ratio 0.79; 95% confidence interval, 0.63 to 0.99 Edoxaban 30 mg versus warfarin: hazard ratio 1.07; 95% confidence interval, 0.87 to 1.31	Edoxaban 60 mg versus warfarin: hazard ratio 0.80; 95% confidence interval, 0.71 to 0.91 Edoxaban 30 mg versus warfarin: hazard ratio 0.47; 95% confidence interval, 0.41 to 0.55

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patients with mechanical heart valves showed increased thromboembolic and bleeding complications in the dabigatran group.

In patients with nonvalvular atrial fibrillation, the left atrial appendage is the site of thrombus formation in at least 95% of patients.[15] Growing evidence supports left atrial appendage occlusion as an alternative to oral anticoagulation in patients with atrial fibrillation. Data from the PREVAIL (Evaluation of the WATCHMAN Left Atrial Appendage [LAA] Closure Device in Patients With

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Study	Patient population	Comparator groups	Stroke or systemic embolism	Major hemorrhage
AVERROES (randomized controlled)	Mean age: 70 years Mean $CHADS_2$ score: 2.0 History of stroke or TIA: 14%	Apixaban 5 mg Aspirin 81 mg to 324 mg	Apixaban versus aspirin: hazard ratio 0.45; 95% confidence interval, 032 to 0.62	Apixaban versus aspirin: hazard ratio 1.13; 95% confidence interval, 0.74 to 1.75
PREVAIL-AF and PROTECT AF: 5-year follow-up	Mean age: 73 years Mean $CHADS_2$ score: 2.3 Mean TTR: 62% History of stroke or TIA: 23%	WATCHMAN Warfarin	WATCHMAN versus warfarin: hazard ratio 0.96; 95% confidence interval, 0.60 to 1.54	WATCHMAN versus warfarin (including procedural bleeding): hazard ratio 0.91; 95% confidence interval, 0.64 to 1.29 WATCHMAN versus warfarin (excluding procedural bleeding): hazard ratio 0.48; 95% confidence interval, 0.32 to 0.71
PRAGUE-17	Mean age: 73 years Mean CHA_2DS_2-VASc score: 4.7 History of stroke: 32.1%	WATCHMAN DOACs	WATCHMAN versus DOACs: All stroke or TIA, WATCHMAN versus DOACs: hazard ratio 1.00; 95% confidence interval, 0.40 to 2.51	WATCHMAN versus DOACs: Major and nonmajor bleeding, WATCHMAN versus DOACs: hazard ratio 0.53; 95% confidence interval, 0.26 to 1.06
AMULET-IDE	Mean age: 75 years Mean CHA_2DS_2-VASc score: 4.6 History of stroke: 19.0%	Amulet WATCHMAN	Amulet versus WATCHMAN: All stroke, Amulet versus WATCHMAN: hazard ratio 0.81; 95% confidence interval, 0.47 to 1.39	Amulet versus WATCHMAN: hazard ratio 1.07; 95% confidence interval, 0.80 to 1.43

[a] Reprinted with permission from Mac Grory B, et al, Circulation Research.[8] © 2022, Wolters Kluwer Health.

$CHADS_2$ = **c**ongestive heart failure, **h**ypertension, **a**ge 75 years or older, **d**iabetes mellitus, and previous **s**troke/TIA; CHA_2DS_2VASc = $CHADS_2$ plus **v**ascular disease, **a**ge 65 to 74 years, and **s**ex **c**ategory (female); DOACs = direct oral anticoagulants; TIA = transient ischemic attack; TTR = time in therapeutic range.

Atrial Fibrillation Versus Long Term Warfarin Therapy) and PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trials demonstrated that left atrial appendage occlusion may provide stroke prevention and lead to a lower risk of major hemorrhage and death (TABLE 4-1).[16] Furthermore, the PRAGUE-17 (Interventional Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in High-risk Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage occlusion is noninferior to direct oral anticoagulant treatment in terms of a broad composite endpoint in patients with nonvalvular atrial fibrillation (TABLE 4-1).[17] Furthermore, data from AMULET-IDE (Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial) suggest that the Amulet left atrial appendage occlusion device is noninferior to WATCHMAN (TABLE 4-1).[18] However, no trials have assessed the noninferiority of left atrial occlusion versus anticoagulation for the endpoint of stroke. Therefore, at this time, left atrial appendage occlusion is reserved for patients who are deemed to be at high risk for long-term oral anticoagulation therapy but are candidates for 45 days of anticoagulation therapy.[19] The ongoing CHAMPION-AF (WATCHMAN FLX Versus NOAC for Embolic ProtectION in the Management of Patients With Non-Valvular Atrial Fibrillation) and CATALYST (Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants) trials are comparing WATCHMAN FLEX (a newer version of WATCHMAN) and Amulet, respectively, to direct oral anticoagulants in patients with nonvalvular atrial fibrillation. These trials will be essential to determine if the use of left atrial appendage occlusion is a viable initial treatment in patients with nonvalvular atrial fibrillation.

In patients with acute cardioembolic stroke in the setting of atrial fibrillation, studies have shown that parenteral anticoagulation with heparin or low-molecular-weight heparin is associated with increased risk of intracranial hemorrhage, without a reduction in the risk of ischemic recurrence.[20,21] Therefore, in most patients with acute cardioembolic stroke, oral anticoagulation, preferably with direct oral anticoagulants,[21] is generally started without bridging with heparin or low-molecular-weight heparin.

The RAF (Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation) study showed that it is reasonable to start warfarin 4 to 14 days after a cardioembolic stroke, but more recent observational studies suggest that starting a direct oral anticoagulant 0 to 3 days after an ischemic stroke does not carry increased risk of hemorrhage when compared with starting after 3 days.[22-24] Current American Heart Association/American Stroke Association guidelines suggest initiating anticoagulation after 2 to 14 days in patients at low risk for hemorrhagic conversion and beyond 14 days for those at high risk.[19] Ongoing clinical trials will help determine the optimal timing of anticoagulation initiation in patients with atrial fibrillation–associated acute ischemic stroke.

One challenging scenario clinicians face is when patients have an ischemic stroke despite anticoagulation (CASE 4-1). While anticoagulation is associated with reduced risk of stroke in patients with atrial fibrillation, certain patients have an ischemic stroke despite oral anticoagulation therapy. Studies have shown that one-fourth to one-third of ischemic strokes in patients with atrial fibrillation occur in patients on anticoagulation therapy; these patients have increased stroke

recurrence rates and switching oral anticoagulation does not seem to reduce this risk.[25,26] The management of these patients is challenging (FIGURE 4-2). A detailed history regarding compliance with anticoagulation and drug interactions with other medications is essential. Furthermore, drug levels, coagulation markers, or both can help determine the adequacy of anticoagulation at the time of presentation. Studies suggest performing a comprehensive diagnostic evaluation to identify competing mechanisms such as large artery atherosclerosis, small vessel disease, and cancer-associated hypercoagulability. In patients who develop a breakthrough atrial fibrillation–associated ischemic stroke despite anticoagulation therapy, further research is needed to determine secondary prevention strategies such as the addition of antiplatelet therapy or the combination of left atrial appendage occlusion and oral anticoagulation.[27]

The management of patients with atrial fibrillation and high bleeding risk can be challenging. In patients with atrial fibrillation, studies have shown that patients at increased risk for thrombotic events are also at higher risk for bleeding complications,[28] but in most patients the benefit of oral anticoagulation for stroke prevention outweighs the hemorrhage risk. In patients for whom anticoagulation is contraindicated, small observational studies suggest that left atrial appendage occlusion may be safe[29]; in particular, recent studies suggest that periprocedural dual antiplatelet therapy is equivalent to oral anticoagulation.[30] In patients with a history of intracerebral hemorrhage, particularly deep hemorrhages[31] thought to be related to hypertension, observational studies suggest that anticoagulation resumption may be safe and effective.[32,33] The ongoing randomized trials ASPIRE (Anticoagulation in ICH Survivors for Stroke Prevention and Recovery) and ENRICH-AF (EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation) are comparing the efficacies of direct oral anticoagulants and aspirin in these patients. In patients with a history of extracranial hemorrhage, studies have shown an increased risk of ischemic stroke. Thus, in these patients, anticoagulation should generally be resumed after the bleeding source is successfully treated.[34] On the other hand, left atrial appendage occlusion can be considered in patients with recurrent major extracranial hemorrhage or those whose bleeding source cannot be successfully treated such as those with multiple gastrointestinal arteriovenous malformations.

ATRIAL CARDIOPATHY

Atrial dysfunction or cardiopathy has been proposed as a mechanism of cardioembolic stroke, even in the absence of atrial fibrillation.[35] This is supported by studies showing no temporal relationship between atrial fibrillation and ischemic stroke,[36] suggesting that atrial fibrillation may not be the direct cause of ischemic stroke in all patients with this arrhythmia and that atrial cardiopathy may instead be the pathomechanistic substrate for thrombus formation.[37]

In epidemiological studies, atrial cardiopathy biomarkers such as left atrial enlargement,[38-40] increased p-wave terminal force in lead V1,[41-43] and increased N-terminal pro b-type natriuretic peptide[44,45] have been shown to be associated with increased ischemic stroke risk as well as brain infarcts, particularly those related to embolism. Furthermore, studies have linked atrial fibrosis to ischemic stroke risk in patients with atrial fibrillation[46] and to the embolic stroke of undetermined source (ESUS) stroke subtype.[47,48] While associations with atrial biomarkers and ischemic stroke risk are well established, these were based on studies performed in cohorts where prolonged cardiac monitoring was not

KEY POINTS

- There is growing evidence to support left atrial appendage occlusion as an alternative to oral anticoagulation in patients with atrial fibrillation.
- In patients with acute cardioembolic stroke treated with oral anticoagulants, treatment is generally started without bridging with heparin or low-molecular-weight heparin.
- In patients with atrial fibrillation and ischemic stroke despite anticoagulation a full diagnostic evaluation is important to rule out alternative mechanisms such as small vessel disease or large artery atherosclerosis that are not necessarily related to the atrial fibrillation and thus do not signify anticoagulation failure.

performed and thus it remains uncertain whether these associations are truly independent of concomitant atrial fibrillation which can be brief, paroxysmal, and asymptomatic. Furthermore, cutoff values for these biomarkers that can help risk-stratify patients have not been well established, limiting the clinical utility of such biomarkers.

In addition to atrial biomarkers, certain left atrial appendage biomarkers may indicate an increased risk of atrial thromboembolism. These include high-risk left atrial appendage morphology, reduced left atrial appendage flow velocity, as well as left atrial appendage fibrosis.[15,49,50] Although some reports suggest that left atrial appendage thrombi may form in patients with atrial or left atrial appendage dysfunction but without known atrial fibrillation,[51] most studies of left atrial appendage biomarkers have involved patients with known atrial fibrillation and more studies are needed to investigate these biomarkers as evidence of a direct cause of ischemic stroke in patients without known atrial fibrillation.

Post-hoc analyses of clinical trials suggest that patients with ischemic stroke in the setting of atrial cardiopathy may benefit from oral anticoagulation. For instance, WARSS (Warfarin-Aspirin Recurrent Stroke Study) randomized patients with noncardioembolic stroke to warfarin versus aspirin. The primary outcome of stroke or death at 2 years was similar between the two groups.[52] In a post-hoc analysis of WARSS patients with N-terminal pro b-type natriuretic

CASE 4-1

A 75-year-old man with a history of hypertension and atrial fibrillation presented with a 2-day history of dysarthria. He was taking lisinopril 10 mg once daily and rivaroxaban 20 mg once daily. He reported compliance with his medications and took rivaroxaban daily with dinner. On physical examination, he had a blood pressure of 176/97 mm Hg and a heart rate of 86 beats/min. His general examination was remarkable for an irregularly irregular rhythm and his neurologic examination was pertinent for mild dysarthria and mild right lower facial droop. Upon further history, the patient reported that while at home his blood pressure ranged between 140/70 mm Hg and 160/90 mm Hg. His low-density lipoprotein cholesterol level was 135 mg/dL and his glycosylated hemoglobin level was 5.0%. He underwent a diagnostic evaluation, which revealed a punctate acute infarct in the corona radiata on diffusion-weighted imaging (FIGURE 4-1A) and no significant intracranial or extracranial stenosis on MR angiography (MRA) (FIGURE 4-1B and FIGURE 4-1C). His ECG showed atrial fibrillation and his transthoracic echocardiogram showed normal ejection fraction, moderate left atrial dilation, and moderate left ventricular hypertrophy. His infarct was attributed to small vessel disease in the setting of uncontrolled hypertension. His lisinopril dosage was increased to 40 mg daily with ambulatory blood pressure monitoring and a goal of less than 130/80 mm Hg. He was also started on high-intensity statin therapy for a target low-density lipoprotein cholesterol level of less than 70 mg/dL and recommended for healthy lifestyle measures including diet and regular exercise.

peptide levels greater than 750 pg/mL, warfarin was superior to aspirin in reducing the risk of recurrent stroke or death (hazard ratio 0.30; 95% confidence interval 0.12 to 0.84, $P = .021$).[53] Similarly, the NAVIGATE-ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) trial randomized patients with ESUS to rivaroxaban versus aspirin and showed no difference in recurrent stroke risk between the two groups but significantly higher risk of major hemorrhage in patients randomized to rivaroxaban.[54] A post-hoc analysis of NAVIGATE-ESUS showed that in patients with a left atrial diameter on transthoracic echocardiogram of greater than 4.6 cm, rivaroxaban was superior to aspirin in reducing the risk of recurrence stroke (hazard ratio 0.26; 95% confidence interval 0.07 to 0.94).[55] These markers are also predictors of atrial fibrillation detection after ESUS,[56,57] and since routine cardiac monitoring was not performed in these trials it remains unclear whether the observed benefit of anticoagulation is only in the subset of patients with paroxysmal atrial fibrillation. Furthermore, findings from post-hoc analyses are only hypothesis generating and should be interpreted with caution.

The ATTICUS (Apixaban for Treatment of Embolic Stroke of Undetermined Source) trial compared apixaban to aspirin in patients with ESUS and evidence of risk for cardiac thromboembolism such as a left atrial size greater than 45 mm,

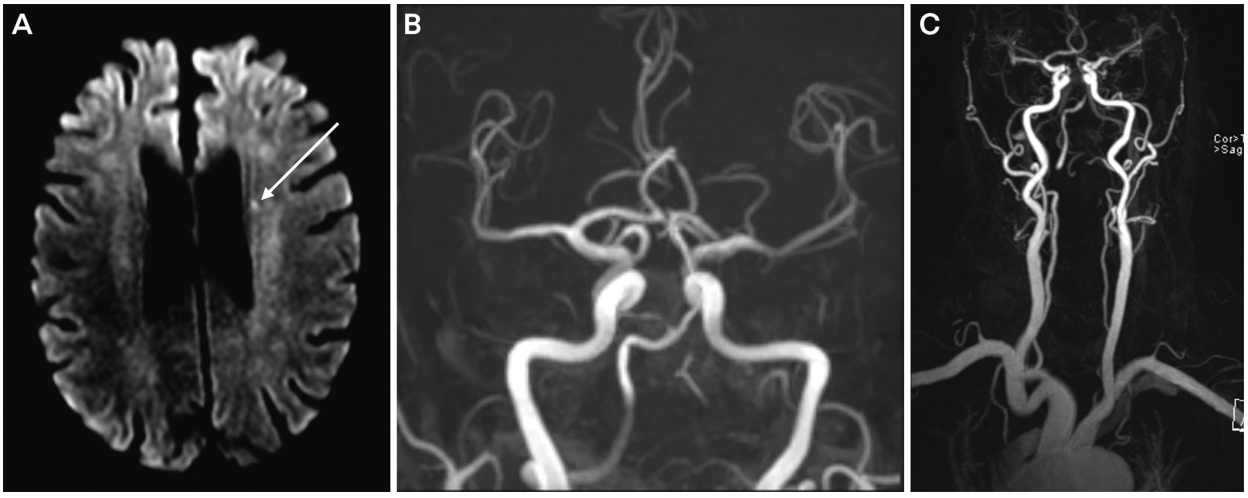

FIGURE 4-1

Imaging of the patient in CASE 4-1. *A*, Diffusion-weighted imaging sequence with punctate infarct in left corona radiata (*arrow*). *B*, MR angiogram (MRA) of the intracranial arteries showing no significant stenosis. *C*, MRA of the extracranial arteries showing no significant stenosis.

COMMENT

This case highlights that in patients with atrial fibrillation and ischemic stroke despite anticoagulation therapy, a full diagnostic evaluation is important to rule out alternative mechanisms such as small vessel disease or large artery atherosclerosis that are not necessarily related to the atrial fibrillation and thus do not signify anticoagulation failure.

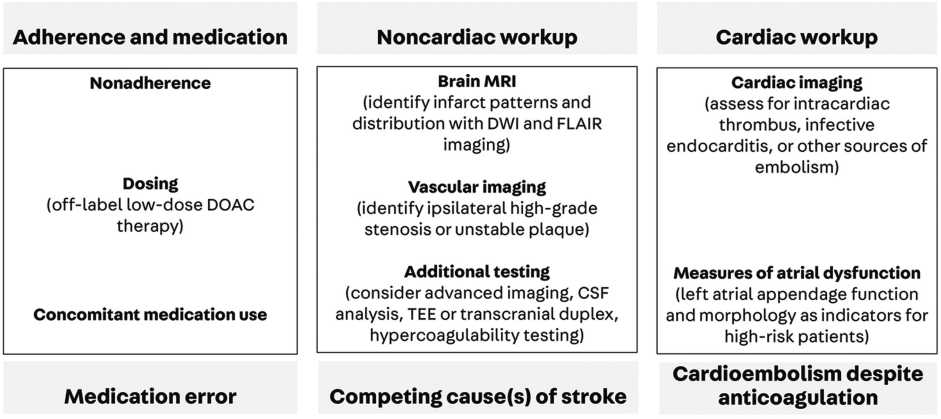
Adherence and medication
Noncardiac workup
Cardiac workup
Nonadherence
Dosing
(off-label low-dose DOAC therapy)
Concomitant medication use
Brain MRI
(identify infarct patterns and distribution with DWI and FLAIR imaging)
Vascular imaging
(identify ipsilateral high-grade stenosis or unstable plaque)
Additional testing
(consider advanced imaging, CSF analysis, TEE or transcranial duplex, hypercoagulability testing)
Cardiac imaging
(assess for intracardiac thrombus, infective endocarditis, or other sources of embolism)
Measures of atrial dysfunction
(left atrial appendage function and morphology as indicators for high-risk patients)
Medication error
Competing cause(s) of stroke
Cardioembolism despite anticoagulation

FIGURE 4-2

Approach to patients with atrial fibrillation and ischemic stroke on anticoagulation therapy. A careful history to assess for medication adherence and dosing and rule out underdosing or poor adherence (left column), followed by a noncardiac workup (middle column) to look for competing noncardioembolic mechanisms as well as a cardiac workup to look for competing cardioembolic causes (right column), are all important steps in managing patients with ischemic stroke who are prescribed anticoagulation therapy.

CSF = cerebrospinal fluid; DOAC = direct oral anticoagulant; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging, TEE = transesophageal echocardiography.

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spontaneous echocardiographic contrast in the left atrial appendage, left atrial appendage flow velocity less than or equal to 0.2 cm/s, atrial high-rate episodes, a CHA_2DS_2VASc score greater than or equal to 4, or patent foramen ovale, and was stopped early after an interim analysis due to futility.[58] The rate of recurrent stroke during follow-up was 6.8% and the atrial fibrillation detection rate in the ATTICUS cohort was reported as 23%.[58] Publication of the full trial results is underway. Since this study was not restricted to atrial cardiopathy, it remains unclear whether empiric anticoagulation is superior to aspirin in patients with atrial cardiopathy and ESUS. The ongoing ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial is randomizing patients with cryptogenic stroke and evidence of one or more atrial cardiopathy biomarkers (ie, left atrial index ≥3 cm/m², N-terminal pro b-type natriuretic peptide >250 pg/mL, or P-wave terminal force in lead V_1 on ECG ≥5000 μV × ms) to apixaban versus aspirin and will shed light on whether oral anticoagulation is safe and effective in patients with cryptogenic stroke and atrial cardiopathy.[59]

PATENT FORAMEN OVALE

Patent foramen ovale (PFO) is a congenital septal defect that is present in nearly 25% of the population[60] and may be associated with a right-to-left shunt, which is more prominent during Valsalva maneuvers. The diagnosis of a PFO is suspected based on the presence of a right-to-left shunt, which highly suggests the presence of a PFO in patients aged 18 years or older. The diagnosis is made based on a positive bubble study (indicative of a right-to-left shunt) on a transthoracic echocardiogram, transesophageal echocardiogram, or transcranial Doppler.[61] The bubble study is enhanced by the Valsalva maneuver and evidence suggests

that transcranial Doppler is superior to transthoracic echocardiography in diagnosing a right-to-left shunt.[62] Transesophageal echocardiography provides the best views of the septum and thus is best at visualizing the PFO and associated abnormalities such as atrial septal aneurysm. The limitations of transesophageal echocardiography are that it is semi-invasive and requires sedation which may limit the patient's ability to perform a Valsalva maneuver, leading to a suboptimal bubble study.[63] When diagnosing a PFO in the setting of an ischemic stroke, it is important to determine whether high-risk features are present which include the degree of shunting (classified as a small shunt [3 to 10 bubbles], medium shunt [10 to 20 bubbles], or large shunt [>20 bubbles])[64] and whether an associated atrial septal aneurysm was present.

Studies have shown an association between PFO and ischemic stroke risk, particularly cryptogenic stroke.[65] One postulated pathomechanism of ischemic stroke in patients with PFO is paradoxical embolism from deep venous thrombosis. This theory is supported by the increased prevalence of pelvic deep venous thrombi in patients with cryptogenic stroke,[66] particularly when a PFO is present.[67] Another postulated pathomechanism is in situ thrombosis at the PFO site.[61]

Due to the substantial prevalence of PFOs in the general population and the low risk of ischemic stroke due to a PFO, it is very important to determine in a patient with ischemic stroke whether the PFO is pathogenic or incidental. The first step is to perform diagnostic testing which includes laboratory tests, brain imaging, intracranial and extracranial vascular imaging, ECG, and cardiac telemetry and at least 30 days of outpatient cardiac rhythm monitoring (in patients aged 40 years or older) to exclude high-risk ischemic stroke mechanisms.[68] In the absence of a competing mechanism, researchers have suggested using the Risk of Paradoxical Embolism (RoPE) score to help determine whether a PFO is pathogenic or incidental (TABLE 4-2[69]).[69] For instance, in patients whose RoPE score is 9 to 10, where the PFO is very likely to be pathogenic, the risk of recurrent stroke at 2 years was 2%.[69] This is contrary to patients with a RoPE score of 0 to 2, indicating that the PFO is likely incidental, in whom the risk of recurrent stroke was 20% at 2 years.[69]

In 2021 investigators introduced the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system, which adds high-risk PFO characteristics (the presence of a substantial shunt and the presence of an atrial septal aneurysm) to the RoPE score.[70] This score classifies the pathogenicity of the PFO as unlikely, possible, or probable and provides added benefit when selecting patients for PFO closure (TABLE 4-3). Both scores will be discussed in the PFO Closure section.

As illustrated in CASE 4-2, the management of patients with ischemic stroke and PFO includes antithrombotic therapy and PFO closure in certain patients. In the presence of deep venous thrombosis, anticoagulation is generally the antithrombotic treatment of choice. The duration depends on whether the deep venous thrombus is provoked or unprovoked. In patients without an indication for anticoagulation use, several studies have compared anticoagulation to antiplatelet therapy in patients with ischemic stroke and PFO.

PICSS (Patent Foramen Ovale in Cryptogenic Stroke Study) was a substudy of WARSS that compared warfarin to aspirin in patients with ischemic stroke and PFO. PICSS showed no benefit from warfarin over aspirin in the risk of stroke or death at 2 years in ischemic stroke patients with PFO (hazard ratio 0.96; 95% confidence interval 0.62 to 1.48, $P = .84$) and in cryptogenic stroke patients with

KEY POINTS

- In addition to atrial biomarkers, certain left atrial appendage biomarkers may indicate an increased risk of atrial thromboembolism.
- Patent foramen ovale (PFO) is a congenital septal defect that is present in nearly 25% of the population and is associated with a right-to-left shunt, which is more prominent during Valsalva maneuvers.
- Evidence suggests that transcranial doppler is superior to transthoracic echocardiography in diagnosing a right-to-left cardiac shunt.
- Transesophageal echocardiography provides the best views of the septum and thus is best at visualizing the PFO and associated abnormalities such as atrial septal aneurysm.
- In patients with cryptogenic stroke in the setting of a PFO, medical and in certain cases surgical management are recommended for secondary stroke prevention.

TABLE 4-2

Risk of Paradoxical Embolism (RoPE) Score[a]

RoPE score components	Score
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age in years	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥70	0

Total RoPE score. For patients with stroke and PFO, points are added with higher scores indicating a higher likelihood of stroke due to PFO.

[a] Modified from Kent DM, et al, Neurology.[69] © 2013 American Academy of Neurology.
PFO = patent foramen ovale; TIA = transient ischemic attack.

TABLE 4-3

PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System

	Likelihood that the PFO is causative of the ischemic stroke	
	RoPE score ≥7	**RoPE score <7**
PFO with straddling thrombus	Definite	Definite
Venous thromboembolism (DVT or PE) preceding the index infarct AND PFO with atrial septal aneurysm OR large shunt	Highly probable	Probable
PFO with atrial septal aneurysm or large shunt	Probable	Possible
PFO with small shunt and without an atrial septal aneurysm	Possible	Unlikely

DVT = deep vein thrombosis; PE = pulmonary embolism; PFO = patent foramen ovale; RoPE = Risk of Paradoxical Embolism.

PFO (hazard ratio 1.17; 95% confidence interval 0.60 to 2.37, P = .65). These differences remained nonsignificant regardless of the PFO shunt size and whether an atrial septal aneurysm was present.

The NAVIGATE-ESUS and RESPECT-ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) trials included patients with PFO. Secondary analysis of NAVIGATE-ESUS showed that in patients with PFO, when compared with aspirin, rivaroxaban was associated with a similar risk of recurrent ischemic stroke (hazard ratio 0.54; 95% confidence interval 0.22 to 1.36) and major bleeding (hazard ratio 2.05; 95% confidence interval 0.51 to 8.18).[71] Furthermore, secondary analysis of the RESPECT-ESUS trial showed that when compared to aspirin, dabigatran was associated with a similar risk of recurrent ischemic stroke (hazard ratio 0.88; 95% confidence interval 0.45 to 1.71) and major bleeding (hazard ratio 0.65; 95% confidence interval 0.15 to 2.74) in patients with PFO.[72]

CASE 4-2

A 42-year-old woman with no known medical history was brought to the emergency department by ambulance after she developed left-sided weakness that occurred during sexual activity. Upon arrival, her blood pressure was 125/85 mm Hg and her blood glucose level was 128 mg/dL. Her general physical examination was within normal limits, and her neurologic examination was pertinent for left facial droop, mild dysarthria, mild left hemiparesis with 4/5 strength in her left arm and left leg, and sensory extinction on the left side.

She underwent a head CT that showed no hemorrhage and CT angiography of the head and neck that showed a right M1 segment occlusion. She was treated with IV alteplase and was taken for mechanical thrombectomy with successful reperfusion and full resolution of her deficits except for mildly reduced dexterity in her left hand and foot. She underwent a diagnostic evaluation including an MRI showing an acute infarction in the right middle cerebral artery territory. MR angiography (MRA) of the head and neck with fat-suppressed images showed no evidence of acute dissection. Laboratory testing for antiphospholipid antibodies was negative at two time points 12 weeks apart. An ECG showed normal sinus rhythm and cardiac telemetry showed no evidence of atrial fibrillation. A 30-day cardiac monitor showed no evidence of atrial fibrillation. A transthoracic echocardiogram showed a large right-to-left shunt and a patent foramen ovale was visualized by transesophageal echocardiogram. She was started on aspirin 81 mg once daily and underwent successful patent foramen ovale closure without complications and has been stroke free for 3 years.

COMMENT

This case illustrates that in patients with cryptogenic stroke in the setting of a patent foramen ovale, medical and in certain cases surgical management are recommended for secondary stroke prevention.

TABLE 4-4 **Summarized Data From the Six Major Randomized Controlled Trials Looking at PFO Closure Versus Medical Therapy in Patients With Cryptogenic Stroke and PFO[a]**

	CLOSURE 1[74]	PC[75]	RESPECT[76]	CLOSE[77]	GORE REDUCE[78]	DEFENSE PFO[79]
Year of publication	2012	2013	2013	2017	2017	2018
Study population (*N*)	909	414	980	663	664	120
Inclusion criteria						
Age (years)	18-60	<60	18-60	16-60	18-59	18-60
Large shunt (% of patients)	NA	20%	50%	90%	40%	NA
Atrial septal aneurysm (% of patients)	35%	25%	35%	35%	20%	11%
Vascular risk factors						
Hypertension	30%	25%	30%	10%	25%	24%
Diabetes	NA	5%	5%	5%	5%	12%
Active tobacco use	20%	25%	15%	30%	15%	22%
Treatments						
Closure device	STARFlex	AMPLATZER	AMPLATZER	Multiple options	Helex or CARDIOFORM	AMPLATZER
Medical therapy	Antiplatelet or anticoagulation	Antiplatelet or anticoagulation	Antiplatelet or anticoagulation	Antiplatelet only[b]	Antiplatelet only	Antiplatelet or anticoagulation
Outcomes						
Median length of follow-up	2 years	4 years	2.5 years	5.5 years	3 years	2.8 years
Hazard ratio for stroke (95% confidence interval)	0.9 (0.4-2)	0.2 (0-1.7)	NA	0.1 (0-0.3)	0.2 (0.1-0.6)	0% versus 12.9%, *P* = .013
Rate of atrial fibrillation (closure versus medical arm)	5.7% versus 0.7%	2.9% versus 1%	NA	4.6% versus 0.9%	6.6% versus 0.4%	1.7% versus 0%

[a] Modified from Thaler A, et al, Curr Cardiol Rep.[73] © 2021 Thaler A, et al, under exclusive license to Springer Science Business Media, LLC, part of Springer Nature.
[b] One randomized arm took anticoagulation, but no comparison of PFO closure versus anticoagulation was reported.
NA = not available; PFO = patent foramen ovale.

A meta-analysis of four randomized trials showed that antiplatelet and anticoagulant medications led to similar rates of recurrent ischemic stroke in the setting of a PFO (odds ratio 0.70; 95% confidence interval 0.43 to 1.14).[72] Therefore, in the absence of another indication for anticoagulation, antiplatelet therapy may be reasonable for secondary stroke prevention in patients with ischemic stroke in the setting of a PFO.

KEY POINT

- In the absence of another indication for anticoagulation, antiplatelet therapy may be reasonable for secondary stroke prevention in patients with ischemic stroke in the setting of a PFO.

PFO Closure

Several randomized controlled trials tested PFO closure against medical treatment for stroke prevention. These trials are summarized in TABLE 4-4.[73] The initial randomized controlled trials (CLOSURE [Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale], PC [Patent Foramen Ovale and Cryptogenic Embolism], and RESPECT [Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment]) showed no benefit from PFO closure compared to medical treatment (TABLE 4-4). There were several limitations of these trials. For instance, CLOSURE[74] randomized patients with TIA and included TIA as an endpoint, and PC[75] included patients with peripheral arterial embolism. RESPECT[76] was the most selective despite including patients with small right-to-left shunts and without an associated atrial septal aneurysm. While RESPECT showed no significant benefit of PFO closure over medical treatment, patients randomized to PFO closure had fewer events (hazard ratio 0.49; 95% confidence interval 0.22 to 1.11, $P = .08$) and the difference between the two groups was statistically significant in the per-protocol analysis ($P = .03$) and as-treated analysis ($P = .007$).[76] Furthermore, individual patient-level data meta-analysis of the three trials demonstrated a significant benefit in patients with a RoPE score greater than or equal to 7 (hazard ratio 0.31; 95% confidence interval 0.11 to 0.85, $P = .03$) as opposed to those with a RoPE score less than 7 (hazard ratio 0.82; 95% confidence interval 0.42 to 1.59, $P = .56$).

These trials were followed by three further randomized controlled trials with more tailored protocols and inclusion criteria. These are summarized in TABLE 4-4. All three trials (CLOSE [Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence],[77] GORE REDUCE [GORE Septal Occluder Device for Patent Foramen Ovale Closure in Stroke Patients],[78] and DEFENSE PFO [Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale][79]) showed a benefit from PFO closure with higher rates of atrial fibrillation in patients randomized to PFO closure versus medical treatment (TABLE 4-4).

A meta-analysis of the six trials utilizing the RoPE score and the PASCAL classification system showed significant treatment effect heterogeneity across RoPE score and PASCAL classification categories. For instance, the benefit from PFO closure was more pronounced in patients with a RoPE score greater than or equal to 7 (hazard ratio 0.21; 95% confidence interval 0.11 to 0.42) as opposed to those with a RoPE score less than 7 (hazard ratio 0.61; 95% confidence interval 0.37 to 1.00) ($P_{interaction} = .02$).[70] Similarly, the benefit from PFO closure was only seen in patients classified as PASCAL possible (hazard ratio 0.38; 95% confidence interval 0.22 to 0.65) and PASCAL probable (hazard ratio 0.10; 95% confidence interval 0.03 to 0.35), but not PASCAL unlikely (hazard ratio 1.14;

$P_{interaction}$ = .003).[70] Device-associated complications varied based on the PASCAL classification categories: atrial fibrillation beyond day 45 after randomization with a device was 4.41%, 1.53%, and 0.65% in the unlikely, possible, and probable PASCAL categories, respectively.[70]

Given that the trials showing a benefit from PFO closure focused on pathogenic and high-risk PFOs, the inclusion and exclusion criteria of positive trials should be carefully reviewed when considering PFO closure in patients with cryptogenic stroke in the setting of PFO.

A challenging scenario is patients with cryptogenic stroke and PFO who are more than 60 years old, particularly those without vascular risk factors. This is the case since closure trials showing a benefit from PFO closure were limited to patients 60 years or younger, and thus there is no proven benefit from PFO closure in patients who are over 60 years old. That said, PFO closure might still be considered in a very small subgroup of patients over 60 years old with (1) a PFO with high-risk features (substantial shunt, atrial septal aneurysm, or both), (2) no other mechanism is identified despite at least 30 days of cardiac rhythm monitoring, (3) minimal or no vascular risk factors, and (4) PASCAL classification as possible or probable.

ISCHEMIC STROKE IN THE SETTING OF AORTIC DISEASE

Atheromas of the aortic arch, particularly when large or mobile, have been suggested to cause ischemic stroke by artery-to-artery embolism.[68] Studies have shown an association between aortic arch atheromas greater than 4 mm in size with ischemic stroke risk[80,81] as well as recurrent ischemic stroke.[82] This association was more likely to be seen in patients with ascending[80] and mobile or ulcerated aortic atheromas[81] and more so with cryptogenic strokes,[81] suggesting a potentially causal association between the two. While some studies suggest that aortic arch atheromas can be frequently detected by transthoracic echocardiography,[68] transesophageal echocardiography is superior in the diagnosis and grading of atheromas of the aortic arch.[83] Transesophageal echocardiography, however, is semi-invasive and there is accumulating data that noninvasive tests such as CT angiography[84] or cardiac MRI may be used as screening tools.[85]

The secondary prevention of ischemic stroke in the setting of aortic arch atherosclerosis consists of risk factor modification, high-intensity statin therapy, as well as antiplatelet therapy. ARCH (Aortic Arch Related Cerebral Hazard Trial) was the only secondary prevention trial in patients with high-risk aortic arch atheromas.[86] ARCH randomized patients to warfarin versus aspirin and clopidogrel and showed numerically higher ischemic events and major bleeding in patients randomized to warfarin. Furthermore, the rate of vascular death was higher in patients treated with warfarin versus dual antiplatelet therapy (3.4% versus 0%, P = .013).[86] Therefore, antiplatelet therapy is preferred in patients with ischemic stroke in the setting of aortic arch atheroma and no indication for anticoagulation. Furthermore, dual antiplatelet therapy for up to 30 days may be considered in low-bleeding-risk patients, particularly those who meet criteria for the CHANCE (Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events),[87] POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke),[88] or THALES (Acute STroke or Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death)[89] trials. In very rare cases of high-risk aortic atheromas causing recurrent

ischemic stroke despite aggressive medical therapy, surgical treatment may be considered.

Another aortic pathology that can cause ischemic stroke is ascending aortic dissection. Ascending aortic dissection is an extremely rare cause of ischemic stroke associated with high mortality. Spontaneous aortic dissections can be seen in patients with Marfan syndrome, familial thoracic aortic aneurysm or dissection, bicuspid aortic valve, Loeys-Dietz aneurysm syndrome, and vascular Ehlers-Danlos syndrome (Ehlers-Danlos syndrome type IV).[90] In addition to symptoms attributable to cerebral ischemia, most (but not all) patients have chest pain, and some have symptoms attributable to other end-organ ischemia. In patients with acute stroke, ascending aortic dissections can be visualized on vascular imaging with CT angiography of the head and neck (generally performed to rule out an emergent large vessel occlusion). CT angiography of the aorta is the preferred test to detect aortic arch dissection in hemodynamically stable patients. In hemodynamically unstable patients, echocardiography may help identify aortic valve disruption, hemorrhagic pericardial effusion or tamponade, and regional wall abnormalities that can be seen in patients with aortic dissections.

The management of ischemic stroke in the setting of an aortic dissection is challenging and measures to stabilize the dissection can worsen the degree of brain injury. For instance, tight blood pressure control can potentially lead to worsened cerebral perfusion of the ischemic territory and extension of the infarction. Furthermore, the risk of hemorrhagic transformation of the ischemic bed may be further increased in the setting of aortic surgery. Given the high mortality (approximately 60%) of medically treated patients with ascending aortic dissection,[91] emergent surgical repair is generally performed on patients with ascending aortic dissection with or without cerebral ischemia.[90]

ISCHEMIC STROKE IN THE SETTING OF LEFT VENTRICULAR DYSFUNCTION

In patients with systolic heart failure, studies have shown an increased ischemic stroke risk with low left ventricular ejection fraction.[92-94] This risk was shown to be particularly higher with an ejection fraction of less than 15% (adjusted hazard ratio 2.13; 95% confidence interval 1.18 to 3.82, $P = .012$) or in patients with prior history of stroke (adjusted risk ratio 2.66; 95% confidence interval 1.59 to 4.45, $P < .001$).[93,95] The pathophysiology of ischemic stroke in patients with low ejection fraction is presumably due to the formation of left ventricular thrombus which may be detected by a transthoracic echocardiogram with perflutren contrast.[96] Cardiac MRI[85] may be superior to a transthoracic echocardiogram in these patients.[97] Another potential etiology is paroxysmal atrial fibrillation, particularly given that left ventricular systolic dysfunction is associated with atrial fibrillation.[98] Thus, in patients with ischemic stroke and low ejection fraction, prolonged cardiac rhythm monitoring is important to look for atrial fibrillation which would lead to anticoagulation therapy.

In the setting of a low ejection fraction and evidence of a left ventricular thrombus with or without ischemic stroke, patients should receive at least 3 months of anticoagulation with warfarin and until repeat cardiac imaging shows resolution of the thrombus. There are limited data to support using direct oral anticoagulants in such patients.

KEY POINTS

- Atheromas of the aortic arch, particularly when large or mobile, have been suggested to cause ischemic stroke by artery-to-artery embolism.
- The secondary prevention of ischemic stroke in the setting of aortic arch atherosclerosis consists of risk factor modification, high-intensity statin therapy, and antiplatelet therapy.
- Spontaneous aortic dissections can be seen in patients with Marfan syndrome, familial thoracic aortic aneurysm or dissection, bicuspid aortic valve, Loeys-Dietz aneurysm syndrome, and vascular Ehlers-Danlos syndrome (Ehlers-Danlos syndrome type IV).
- In patients with systolic heart failure, studies have shown an increased ischemic stroke risk with low left ventricular ejection fraction.
- In patients with ischemic stroke and low ejection fraction, prolonged cardiac rhythm monitoring is important to look for atrial fibrillation which would lead to anticoagulation therapy.
- In the setting of a low ejection fraction and evidence of a left ventricular thrombus with or without ischemic stroke, patients should receive at least 3 months of anticoagulation with warfarin and until repeat cardiac imaging shows resolution of the thrombus.

The WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial randomized patients with an ejection fraction less than or equal to 35% and sinus rhythm to warfarin (international normalized ratio [INR] 2.0 to 3.5) versus aspirin (325 mg daily). WARCEF showed that when compared to aspirin, warfarin was associated with significantly lower risk of ischemic stroke (hazard ratio 0.52; 95% confidence interval 0.33 to 0.82) but a nonsignificantly higher rate of intracerebral hemorrhage (hazard ratio 2.22; 95% confidence interval 0.43 to 11.66). However, the composite primary outcome of stroke or death was not different between the two (hazard ratio 0.93; 95% confidence interval 0.79 to 1.10).[95] Results were similar in patients with an ejection fraction less than 35% and a history of stroke. Warfarin can still be considered in a subset of patients with low ejection fraction, particularly those with ischemic stroke and an ejection fraction less than 30% who have a reasonable life expectancy. In patients who are started on anticoagulation, a repeat transthoracic echocardiogram is helpful to look for improvement in the ejection fraction after targeted congestive heart failure therapy.

Since direct oral anticoagulants are associated with a lower risk of intracerebral hemorrhage compared to warfarin, it is possible that direct oral anticoagulants will have a net benefit in patients with low ejection fraction. In fact, a post-hoc analysis of the NAVIGATE-ESUS trial investigated the effect of rivaroxaban versus aspirin in patients with ESUS and evidence of moderate to severe left ventricular dysfunction (7.1% of patients enrolled in NAVIGATE-ESUS), which was defined as moderate to severe global impairment in left ventricular contractility, regional wall motion abnormalities, or both. In this analysis, those with left ventricular dysfunction assigned to rivaroxaban versus aspirin had a lower risk of recurrent stroke or systemic embolism (hazard ratio 0.36; 95% confidence interval, 0.14 to 0.93), but those without left ventricular dysfunction did not (hazard ratio 1.16; 95% confidence interval, 0.93 to 1.46) ($P_{\text{interaction}} = .03$).[99]

Given this analysis and the findings from the WARCEF trial, clinical trials are needed to test the safety and efficacy of direct oral anticoagulants when compared to aspirin in patients with left ventricular dysfunction, particularly those with low ejection fraction and with an ischemic stroke.

ISCHEMIC STROKE IN THE SETTING OF MYOCARDIAL INFARCTION

There is an increased ischemic stroke risk in patients with an acute myocardial infarction,[100] and this risk is particularly high in the first 12 weeks after myocardial infarction.[101] The elevated stroke risk appears to be similar in patients with non-ST-elevation myocardial infarction and ST-elevation myocardial infarction, likely due to advances in revascularization strategies.[100,101] Furthermore, analysis from the Cardiovascular Health Study demonstrated that silent myocardial infarction is associated with increased ischemic stroke risk (hazard ratio 1.51; 95% confidence interval 1.03 to 2.21) and this association was limited to nonlacunar ischemic stroke (hazard ratio 2.40; 95% confidence interval 1.36 to 4.22).[102]

In patients with ischemic stroke in the setting of an anterior ST-segment-elevation myocardial infarction, experts recommend consideration of oral anticoagulation with warfarin if deemed safe for 3 months,[103] but this approach lacks high-quality supporting evidence. In patients with myocardial infarction and left ventricular thrombus with or without ischemic stroke, anticoagulation treatment should be initiated for at least 3 months pending resolution of the

thrombus on follow-up cardiac imaging.[19] In all other patients, cardiac monitoring may be beneficial to rule out paroxysmal occult atrial fibrillation and in the absence of atrial fibrillation, antiplatelet therapy is preferred. Given the heightened risk of ischemic stroke in patients with acute myocardial infarction, clinical trials are needed to test the safety of direct oral anticoagulants as an alternative to antiplatelet agents in patients with an acute myocardial infarction but without one of the above-mentioned indications for short-term anticoagulation.

VALVULAR HEART DISEASE

Valvular pathologies that are associated with increased stroke risk are prosthetic heart valves, rheumatic heart disease, and both infective and noninfective endocarditis.

In patients with an ischemic stroke in the setting of a bioprosthetic valve, a diagnostic evaluation is needed to exclude valve failure, thrombosis, or infection as an etiology. In addition, it is important to exclude noncardioembolic non-valve-related ischemic stroke mechanisms such as larger artery atherosclerosis and small vessel disease. In patients with ischemic stroke in the setting of a mechanical heart valve, current guidelines recommend anticoagulation with warfarin with a goal INR of 2.0 to 3.0 for a mechanical aortic valve and 2.5 to 3.5 for a mechanical mitral valve.[102] The addition of low-dose aspirin may be considered, particularly in patients with low bleeding risk, underlying atherosclerotic cardiovascular disease, or both.[104] Furthermore, the RE-ALIGN trial randomized 252 patients with mechanical aortic or mitral valves to dabigatran versus warfarin. This trial was stopped early due to increased rates of thromboembolic and bleeding complications with dabigatran versus warfarin.[14] Therefore, direct oral anticoagulants are not recommended in patients with mechanical heart valves. In patients with bioprosthetic heart valves without evidence of atrial fibrillation, guidelines recommend oral anticoagulation for 3 months to 6 months followed by antiplatelet therapy.[19] In those who have an ischemic stroke while on antiplatelet therapy, the benefit of switching to oral anticoagulation remains uncertain.[19] In these patients, long-term cardiac monitoring is important to exclude concomitant atrial fibrillation which would warrant oral anticoagulation.

Ischemic stroke risk in patients with rheumatic mitral disease has been suggested to be linked to atrial fibrillation,[105] particularly since studies demonstrating such associations did not involve cardiac monitoring.[106] In patients with ischemic stroke in the setting of rheumatic valve disease, a diagnostic evaluation may help exclude other ischemic stroke mechanisms. In the absence of an indication for anticoagulation, workup may include long-term cardiac monitoring to look for atrial fibrillation. In patients with ischemic stroke and rheumatic mitral disease without atrial fibrillation, there is no evidence to support oral anticoagulation therapy. In those with atrial fibrillation and moderate to severe mitral stenosis, warfarin is preferred, whereas in those with atrial fibrillation but without moderate to severe mitral stenosis, direct oral anticoagulants or warfarin could be used.[19]

Ischemic stroke is an established complication of infective or noninfective aortic or mitral valve endocarditis and in patients with infective endocarditis, data suggest that ischemic stroke risk is heightened between 4 months before the endocarditis diagnosis is made and 5 months after diagnosis.[107] In patients with

KEY POINTS

- Clinical trials are needed to test the safety and efficacy of direct oral anticoagulants when compared to aspirin in patients with left ventricular dysfunction, particularly those with low ejection fraction and with an ischemic stroke.
- There is an increased ischemic stroke risk in patients with an acute myocardial infarction, and this risk is particularly high in the first 12 weeks after myocardial infarction.
- In patients with myocardial infarction and left ventricular thrombus with or without ischemic stroke, anticoagulation treatment should be initiated for at least 3 months pending resolution of the thrombus on follow-up cardiac imaging.
- Valvular pathologies that are associated with increased stroke risk are prosthetic heart valves, rheumatic heart disease, and both infective and noninfective endocarditis.
- In patients with an ischemic stroke in the setting of a bioprosthetic valve, a diagnostic evaluation is needed to exclude valve failure, thrombosis, or infection as an etiology.
- Direct oral anticoagulants are not recommended in patients with mechanical heart valves.

KEY POINTS

- Ischemic stroke risk in patients with rheumatic mitral disease has been suggested to be linked to atrial fibrillation, particularly since studies demonstrating such associations did not involve cardiac monitoring.
- In patients with marantic endocarditis in the setting of cancer, treatment entails management of the underlying malignancy as well as antithrombotic therapy.
- In patients with ischemic stroke in the setting of Libman-Sacks endocarditis, guidelines suggest anticoagulation with heparin or low-molecular-weight heparin instead of oral anticoagulation if deemed safe, but these suggestions lack high-level supporting evidence.
- Left-sided cardiac tumors such as atrial myxomas and fibroelastomas are very rare causes of ischemic stroke.
- While the optimal stroke prevention strategy for patients with ischemic stroke and left sided cardiac tumors is unknown, in addition to antithrombotic treatment, surgical tumor resection is a reasonable approach.

ischemic stroke, infective endocarditis is typically suspected in those who have clinical or laboratory concern for bacteremia (modified Duke criteria),[108] whereas noninfective endocarditis is typically seen in patients with systematic lupus erythematosus (Libman-Sacks endocarditis) or malignancy (marantic endocarditis). The diagnosis is confirmed by visualization of a valvular vegetation on echocardiography, particularly transesophageal echocardiography.[109] Infarct patterns may differ between infective and noninfective endocarditis, with one study suggesting that any infarct pattern can be seen with infective endocarditis, whereas disseminated punctate lesions are the dominant infarct pattern in noninfective endocarditis.[110] For patients with ischemic stroke and infective endocarditis, noninvasive intracranial vascular imaging to screen for mycotic aneurysms with or without a diagnostic angiogram should be considered.[109] The treatment of endocarditis depends on the etiology. For infective endocarditis, treatment entails IV antimicrobial treatment for at least 6 weeks as well as consideration for surgery in a subgroup of patients. Surgery is typically considered in those with valvular dysfunction causing heart failure, complications (eg, paravalvular extension), or poor response to antimicrobial therapy. Antithrombotics are generally contraindicated in the acute setting.[109] In patients with marantic endocarditis in the setting of cancer, treatment entails treating the underlying malignancy as well as antithrombotic therapy. In these patients, some experts suggest direct oral anticoagulants or parenteral anticoagulation with heparin or low-molecular-weight heparin and others only suggest parenteral anticoagulation with heparin or low-molecular-weight heparin,[104] but a high level of evidence supporting those treatments is lacking.[111] In patients with ischemic stroke in the setting of Libman-Sacks endocarditis, guidelines suggest anticoagulation with heparin or low-molecular-weight heparin instead of oral anticoagulation if deemed safe,[104] but these suggestions lack high levels of supporting evidence.[19] Moreover, in patients with systemic lupus erythematosus, the occurrence of valve lesions is independent of disease activity and may occur at any time;[112] thus, it is unclear whether control of disease activity is effective in stroke prevention in such patients and antithrombotic therapy is usually recommended regardless of the disease activity. In certain patients with noninfectious endocarditis, valve replacement surgery may be considered.

ISCHEMIC STROKE IN THE SETTING OF LEFT HEART TUMORS

Left-sided cardiac tumors such as atrial myxomas and fibroelastomas are very rare causes of ischemic stroke.[113,114] Left atrial myxomas can lead to ischemic stroke via embolization of thrombus, tumor, or both,[115] whereas aortic valve papillary fibroelastomas, particularly those that are mobile, are thrombogenic, increasing the risk of thromboembolism.[113,116]

While the optimal stroke prevention strategy for patients with ischemic stroke and left-sided cardiac tumors is unknown, in addition to antithrombotic treatment, surgical tumor resection is a reasonable approach.[19,117]

CONCLUSION

Several pathologies can lead to cardioembolic stroke, including atrial fibrillation, aortic arch atheroma, patent foramen ovale, left ventricular dysfunction, and many others. Secondary stroke prevention strategies differ across these

heterogeneous mechanisms. Therefore, a thorough diagnostic evaluation is essential to determine cardioembolic causes of stroke. In addition to risk factor management and lifestyle modifications, identification and targeting of the underlying cardioembolic stroke mechanisms will lead to improved stroke prevention strategies in these patients.

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